REMARKS

Claims 101-114 and 124-129 are pending in this application. In the Advisory Action mailed October 28, 2003, the Examiner withdrew the finality of the last Office Action and withdrew the rejection of claims 108-114 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Claims 108-114 and 127-129 are allowed. Claims 101, 104, 105, and 124 are newly rejected under 35 U.S.C. § 102(b) or under 35 U.S.C. § 103(a). Claims 102, 103, 106, 107, 125, and 126 are objected to as being dependent on rejected claims, but the Examiner states that these claims would be allowable if rewritten in independent form to include the limitations of the base claim and any intervening claim.

Claim 107 has been amended to correct a lack of antecedent basis for the word "means." No new matter is added by this amendment.

The Claims Are Not Anticipated by Metzker

Claims 101, 104, 105, and 124 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,728,529 to Metzker et al. ("Metzker"). (Office Action mailed October 28, 2003, page 3.) According to the Examiner, Metzker "discloses methods for the use of a class of dyes for improved DNA sequencing by the chain termination method of DNA sequencing, and internal labelling of polynucleotides by enzymatic incorporation of fluorescently-labeled ribonucleotides or deoxyribonucleotides." *Id.* The Examiner asserts that these methods are "viewed to be inclusive of the method of instant claim 101 where labeled fragments are obtained[,] separated by size and sequence determined." *Id.*

Applicants respectfully traverse. In order to anticipate, a prior art reference must contain each and every element of the rejected claim. *See* M.P.E.P. § 2131; *Verdegaal*

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Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987). Here, claim 101 (and claims 104, 105, and 124, which depend therefrom) recites "[a] method for determining a polynucleotide sequence, comprising" five steps: (i) annealing a primer to a template polynucleotide; (ii) extending the primer in the presence of a mixture of unlabeled dNTPs and at least one dye-labeled ribonucleotide so that primer extension products containing at least one dye-labeled ribonucleotide are formed; (iii) cleaving the primer extension products to form a plurality of labeled fragments; (iv) separating the extension products by size; and (v) detecting the fragments to determine the polynucleotide sequence.

Metzker neither teaches nor suggests a method of DNA sequencing with all of these elements. Instead, as the Examiner acknowledges, Metzker discloses a method for DNA sequencing by the chain termination method. (Office Action, page 3.) In Metzker's DNA sequencing method, it is the 3'-dideoxynucleotide (i.e., the "chain terminator") that is labeled with a fluorescent dye. For example, Metzker's claim 1 recites, in relevant part:

> forming a mixture of a first, a second, a third, and a fourth class of polynucleotides, each polynucleotide in the first class having **a 3'-terminal dideoxyadenosine triphosphate**, said 3'-terminal dideoxyadenosine triphosphate being attached at the 7 position of the 7-deazapurine to a 3-amino-1-propynyl linker, said linker then **attached to a BODIPY® dipyrromethene boron difluoride linker at a 3 position of a first BODIPY® fluorophore** that contains at least one reactive functional group; each polynucleotide in the second class having **a 3'-terminal dideoxycytidine triphosphate**, said 3'-terminal dideoxycytidine triphosphate being attached at the 5 position of the pyrimidine to a 3-amino-1-propynyl linker, said linker then **attached to a BODIPY® linker at a 3 position of a second BODIPY® fluorophore** that contains at least one reactive functional group; each polynucleotide in the third

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> class having a **3'-terminal dideoxyguanosine triphosphate**, said 3'-terminal dideoxyguanosine triphosphate being attached at the 7 position of the 7-deazapurine to a 3-amino-1-propynyl linker, said linker then **attached to a BODIPY® linker at a 3 position of a third BODIPY® fluorophore** that contains at least one reactive functional group; each polynucleotide in the fourth class having **a 3'-terminal dideoxythymidine triphosphate**, said 3'-terminal dideoxythymidine triphosphate being attached at the 5 position of the pyrimidine to a 3-amino-1-propynyl linker, said linker then **attached to a BODIPY® linker at a 3 position of a fourth BODIPY® fluorophore** that contains at least one reactive functional group;

(emphasis added); *see also* Metzker, col. 6, lines 11-38; col. 9, lines 34-61.

Metzker neither teaches nor suggests a method of DNA sequencing using fluorescently labeled ribonucleotides as recited by claim 101. Instead, Metzker discloses only a method for sequencing DNA using fluorescently labeled dideoxynucleotides. For this reason, Metzker cannot anticipate claim 101.

Moreover, the only method of DNA sequencing disclosed as being part of his invention relies upon chain termination by dideoxynucleotides to produce the fragments analyzed.[1] *See id.* The method of claim 101 is fundamentally different. It does not rely on fragments produced by dideoxynucleotide chain termination, but rather on fragments produced by cleaving extension products at the site of fluorescent ribonucleotide incorporation. For this reason too, Metzker cannot anticipate claim 101.

Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 101, 104, 105, and 124 under 35 U.S.C. § 102(b).

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[1] Metzker also mentions sequencing by the chemical degradation method of Maxam and Gilbert and by hybridization-based methods in the "Background" section of the patent. *See* col. 2, lines 9-12

The Claims Are Not Obvious Over Metzker

The Examiner also rejects claims 101, 104, 105, and 124 under 35 U.S.C. 103(a) as allegedly being unpatentable over Metzker. (Office Action, page 3.) According to the Examiner, Metzker discloses methods for internally labeling RNA or DNA "fragments" by the enzymatic incorporation of fluorescent ribonucleotides or deoxyribonucleotides. *Id.*, page 4. The Examiner continues, "[t]he labeled fragments may then be analyzed which is viewed to be inclusive of the cleavage, separation and detecting steps of the instant invention." *Id.*

Applicants respectfully traverse. In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must establish three elements. First, the Examiner must point to a suggestion or motivation, either in the prior art or in the general body of knowledge, to modify or combine the prior art. Second, there must be a reasonable expectation of success in making the suggested modification. Third, the prior art as modified or combined must teach or suggest all limitations of the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142.

As an initial matter, Applicants note that Metzker does not disclose a method for labeling DNA or RNA "fragments." Rather, Metzker discloses methods for labeling "polynucleotides" with either fluorescent ribonucleotides or fluorescent deoxyribonucleotides. *See*, e.g., Metzker, claims 7 and 12. In fact, Metzker neither teaches nor suggests that "fragments" of fluorescently labeled polynucleotides should be prepared for any purpose, including DNA sequencing. Instead, Metzker indicates that his labeling methods using fluorescent ribonucleotides are intended to "distinguish

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polynucleotides having different ribonucleotides" in a mixture. *See, e.g.*, Metzker, col. 10, lines 6-46.

Moreover, despite the Examiner's assertion to the contrary, Metzker neither teaches nor suggests that the analysis of polynucleotides labeled with fluorescent ribonucleotides encompasses the *cleavage* of the labeled nucleic acids as required by claim 101. Metzker simply discloses that the labeled polynucleotides are "electrophoretically separated on a gel by size." Metzker, col. 10, lines 40-41. There is no mention of a cleavage step and the Examiner has provided no legitimate basis for reading such a step into Metzker's disclosure.

In summary, the Examiner provides none of the elements necessary to support a *prima facie* case of obviousness. First, the Examiner points to no suggestion or motivation, either in the prior art or in the general body of knowledge, to modify Metzker's methods into a method for DNA sequencing based on cleaving primer extension products at the sites of fluorescent ribonucleotide incorporation. Second, because Metzker describes only a method for chain termination sequencing (see discussion of the section 102(b) rejection), the Examiner points to no basis for concluding that one of ordinary skill in the art would reasonably expect a sequencing method based on cleaving primer extension products at the sites of fluorescent ribonucleotide incorporation to work.[2] Third, the Examiner points to no teaching or suggestion to add a cleavage step to the methods of Metzker.

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[2] The question is not whether one of ordinary skill in the art would reasonably expect to be successful in cleaving primer ribonucleotide-containing extension products. Rather, the question is whether one of ordinary skill in the art would reasonably expect to be successful in determining the sequence of the template.

Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 101, 104, 105, and 124 under 35 U.S.C. 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 28, 2004 By: 

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